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2415 C3H
(56) Documents cited
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(58) Field of search
C3H

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(54) Genetic engineering

(57) It has been a problem to find an alternative, less time-consuming, and more reliable source of factor IX, a polypeptide which is essential to the human blood-clotting process and necessary for the treatment of patients with Christmas disease. In order to aid in the solution of the problem, there is provided recombinant DNA containing a DNA sequence occurring in the human factor IX genome, and includes recombinant DNA comprising substantially the whole sequence of human factor IX genome, which is inserted in a cloning vehicle a transformed into a host, such *Escherichia coli*. Other fragme the sequence have also been and the invention includes DN molecules comprising part or human factor IX DNA. There is described cDNA derived from factor IX RNA. Uses include th provision of an intermediate o in the genetic engineering of a IX polypeptide precursor and t manufacture of the factor IX polypeptide, and in making pr use in diagnosing the presenc normal or abnormal factor IX patients with Christmas disea

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1st amino acid sequence :		70 75 Glu-Cys-Trp-Cys-Gln-Ala
mRNA :	5'	GA^{A}_{G} UG^{U}_{C} UGG UG^{U}_{C} CA^{A}_{G} GCN 3'
Deoxyoligonucleotides synthesized :	3'	CT^{T}_{C} AC^{A}_{G} ACC AC^{A}_{G} GTT CG (oligo N2A)
	3'	CT^{T}_{C} AC^{A}_{G} ACC AC^{A}_{G} GTC CG (oligo N2B)

2nd amino acid sequence :		348 352 His-Met-Phe-Cys-Ala
mRNA :	5'	CA^{U}_{C} AUG UU^{U}_{C} UG^{U}_{C} GCN 3'
Deoxyoligonucleotides synthesized :		GT^{A}_{G} TAC AA^{A}_{G} AC^{A}_{G} CG (oligo N1)

Fig. 1

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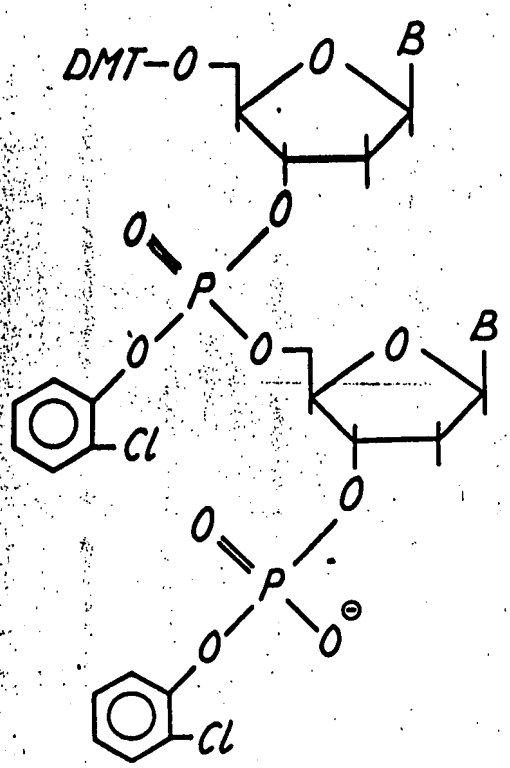


Fig. 2

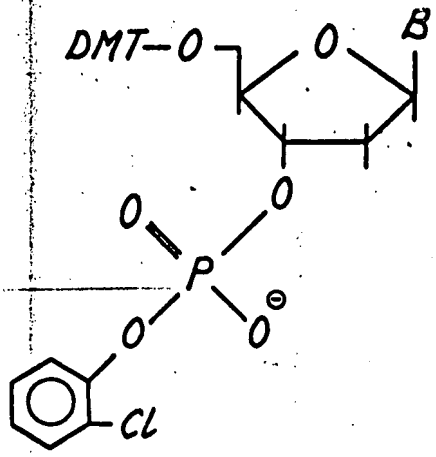
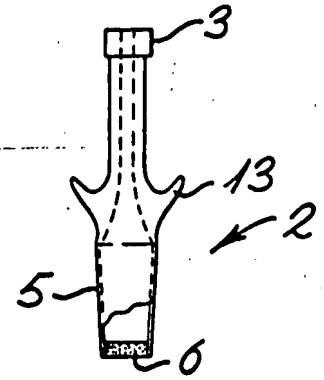


Fig. 3



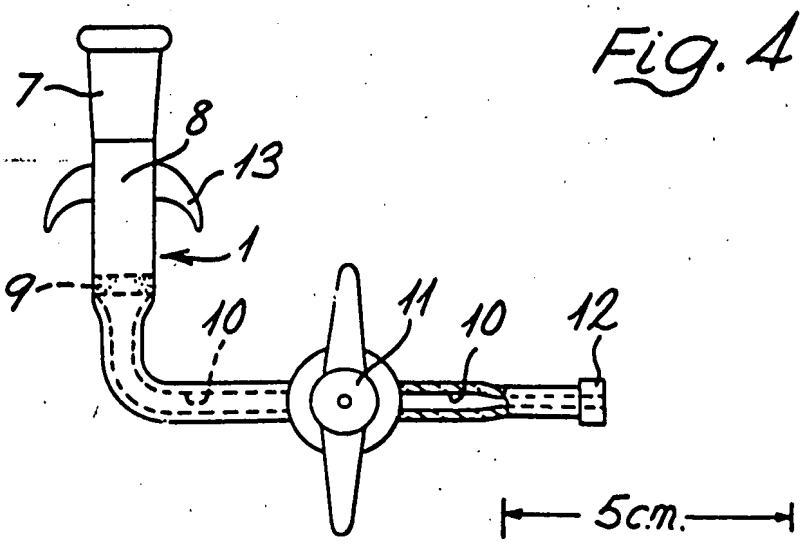


Fig. 4

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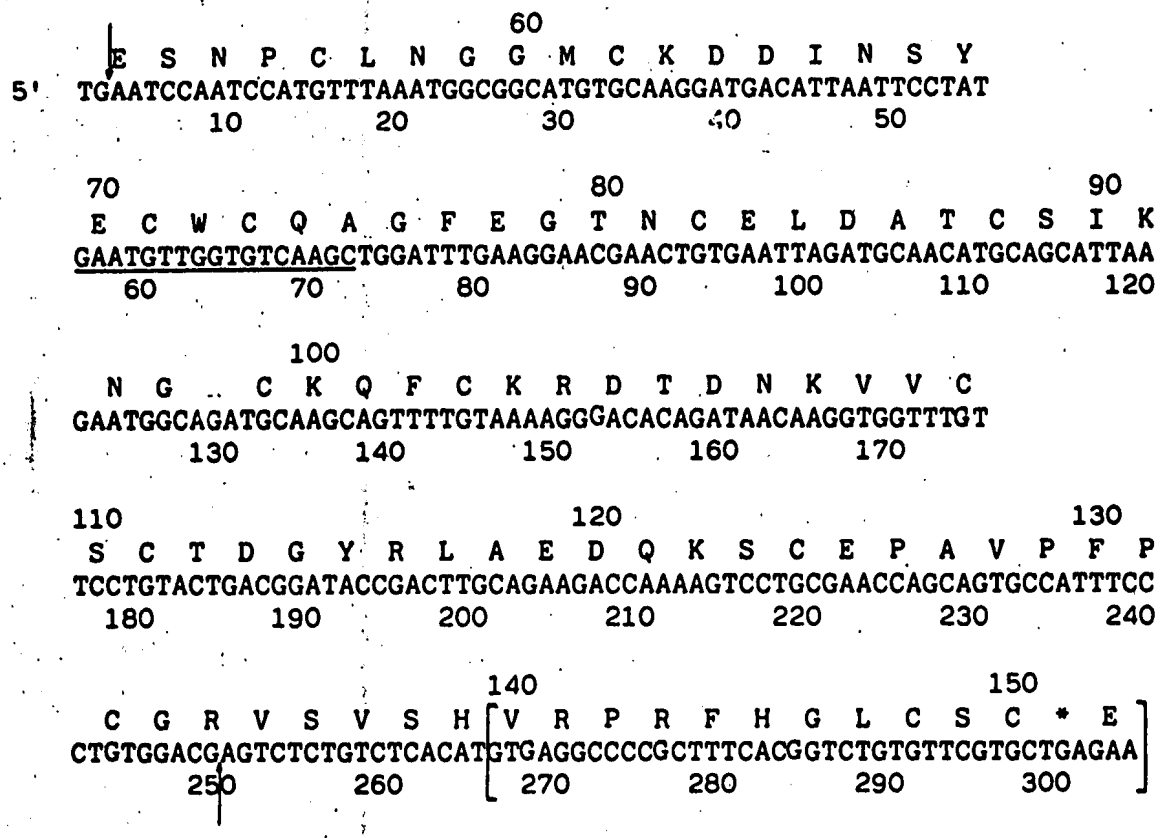

Fig. 5

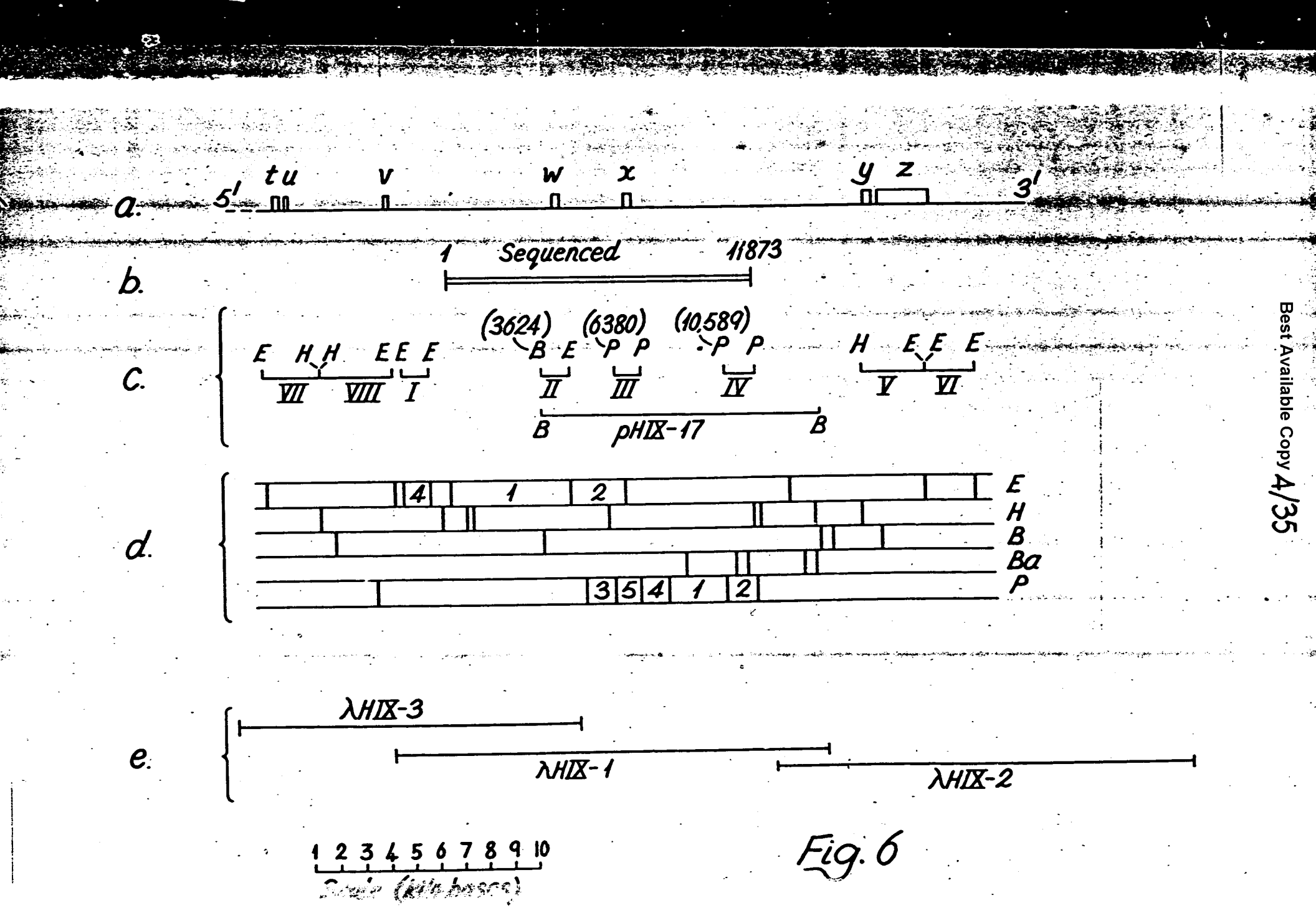

Fig. 6

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GAATTCCTTGTGCCATTATTTTATTTCTGGAATCTTCAGCCTTTTAGCTGAGGGCAAAAGATTGCTGATT..GGAAGCAATATTTCCCACCTCCTGCGCAAAACAAGCCAAAGATCAACAG
        10        20        30        40        50        60        70        80        90       100       110       120

CAGCAGCAACATACTGAGCCCTAAAG-GGTGACAAATCTGGAGAATGATACAGAGGTCTGGTTACTTCTTAGCCAATGACACAGAATCACAATTGAGAAAACACAGAGTTTATTCATTCC
       130       140       150       160       170       180       190       200       210       220       230       240

CATTGTGCATGCCCTGACAAACCAAGCTGCACCTTTCGTAACTTATCACAATCTCATATTGACGGAACACTTTCTACAGGTAATGTTTAGTTTGGCTGAACACTTTAGCAATTGCTTCTG
       250       260       270       280       290       300       310       320       330       340       350       360

TAGCAACAAAATGATAGCTAGTAACAGAAAAGTTCAGGAATATTACCACTGTTAGTGAGGAGAAAGGCCTTTTAATTAATTAATTAATTAATTAATAGAACCAAGTACCATCTTTTTG-A
       370       380       390       400       410       420       430       440       450       460       470       480

TCATGCCCTTAGTGAATTATTGGTAGCAAAGGTTAAAGCTCAAGCTGGTTCCTTTGTCCCCTG-CAACAGTTGATTT-CCTCCCTTTATCTCCTGAAGTACCGTAAG-ACTAAGAGCCAA
       490       500       510       520       530       540       550       560       570       580       590       600

TTATTACATTTG-TCATGTCAGCTATATGTAAAATAGAGTTTAAAAGTTTAGATTCATCACTCAAAAATTCATATTCTCCAAAACCATACAGTCACTCTGTTAGCCTGTGTTCCCCCAGA
       610       620       630       640       650       660       670       680       690       700       710       720

AAAAAAGTCACAAGCTTATTTATTAACATGTGCAATCCCA-GGGGCAAGAGAAAGGAACTGAAGAGTGAGGCAGAAAGGAAAAGAAAG-CAATAAGAGGATGAGTTATCAAACTACTCGT
       730       740       750       760       770       780       790       800       810       820       830       840

TTCTAACAGCAACTGATTGCTTAACTTCCTAGGACTGTCTCCAATAAGTCAAATTG-CCTCAGGTTAGCCACCTGAGTGGAAAGAAGCGGTGAAAGAATTTGTCTGTCAGTATCTGTCTC
       850       860       870       880       890       900       910       920       930       940       950       960

TCATTGGTTAGAAGTTCGACTTATGGGGAATTAACTC-CTCACATTTCCTAGTTGGATATGCTTGGGTACAGAGGGT-ATAGTAGCATTACTGCCTCA-GCATGAACAGGGAAGCTTTCA
       970       980       990      1000      1010      1020      1030      1040      1050      1060      1070      1080
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FIG. 7a

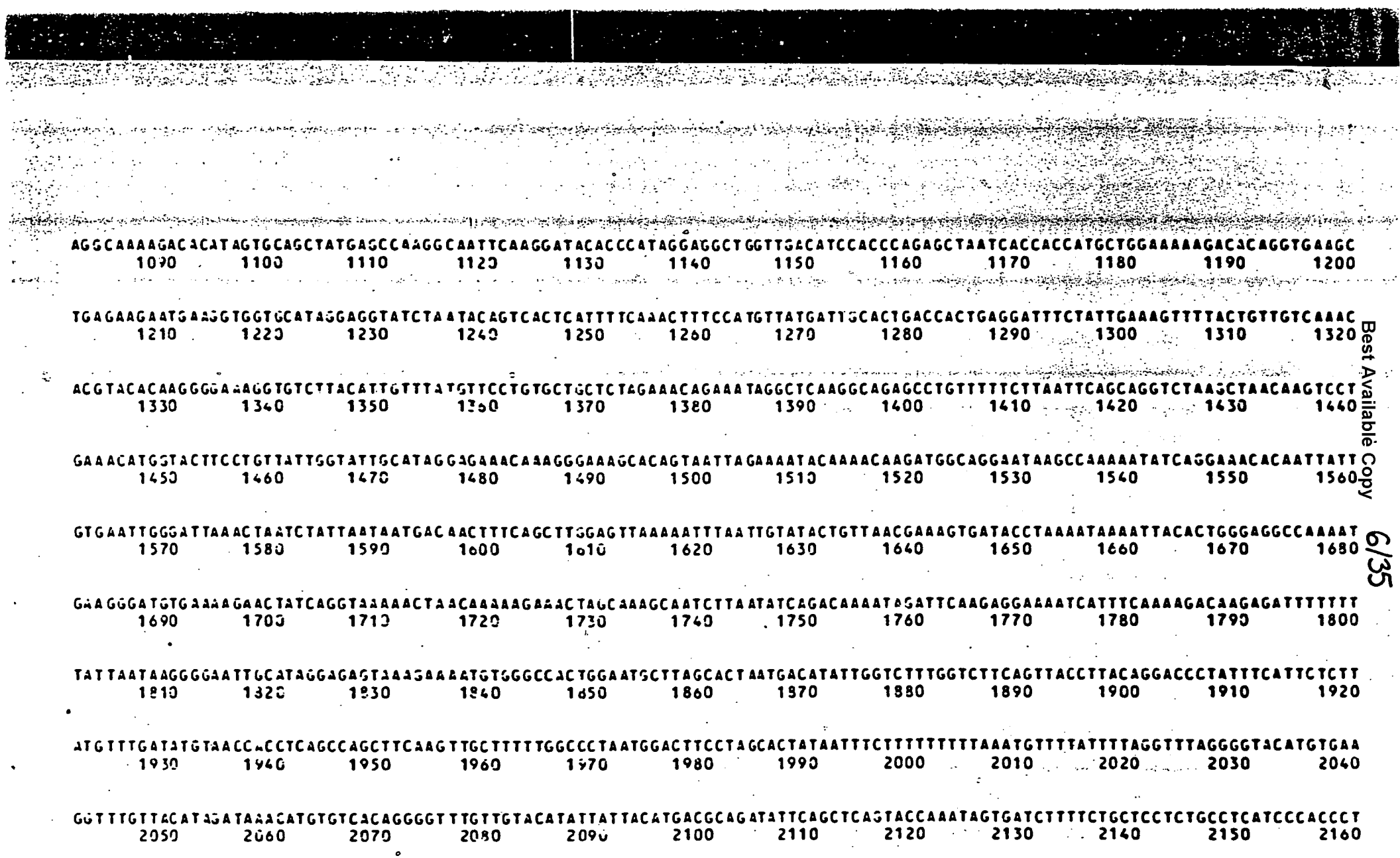

FIG. 7b

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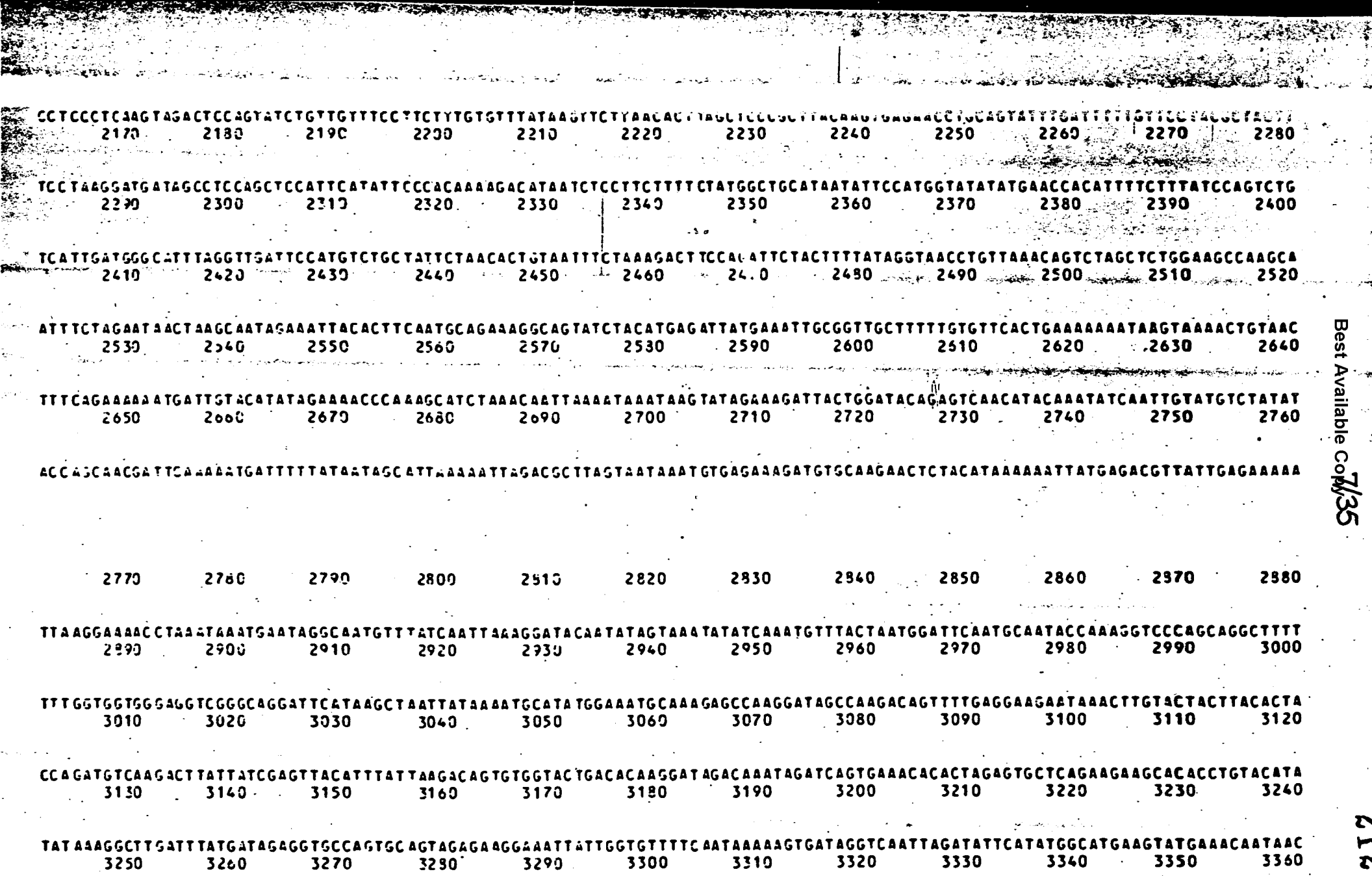

FIG. 7c

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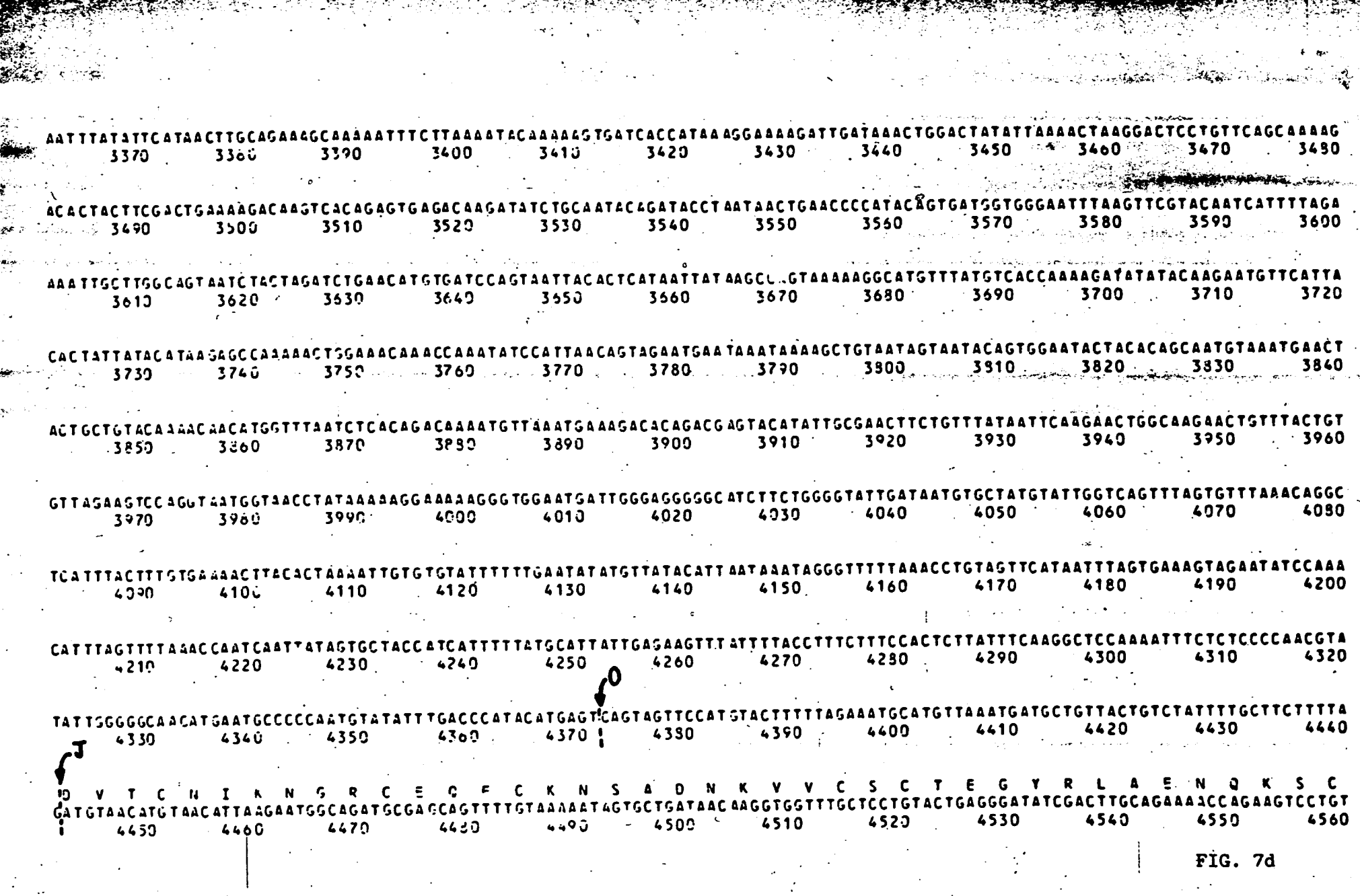

FIG. 7d

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FIG. 7e

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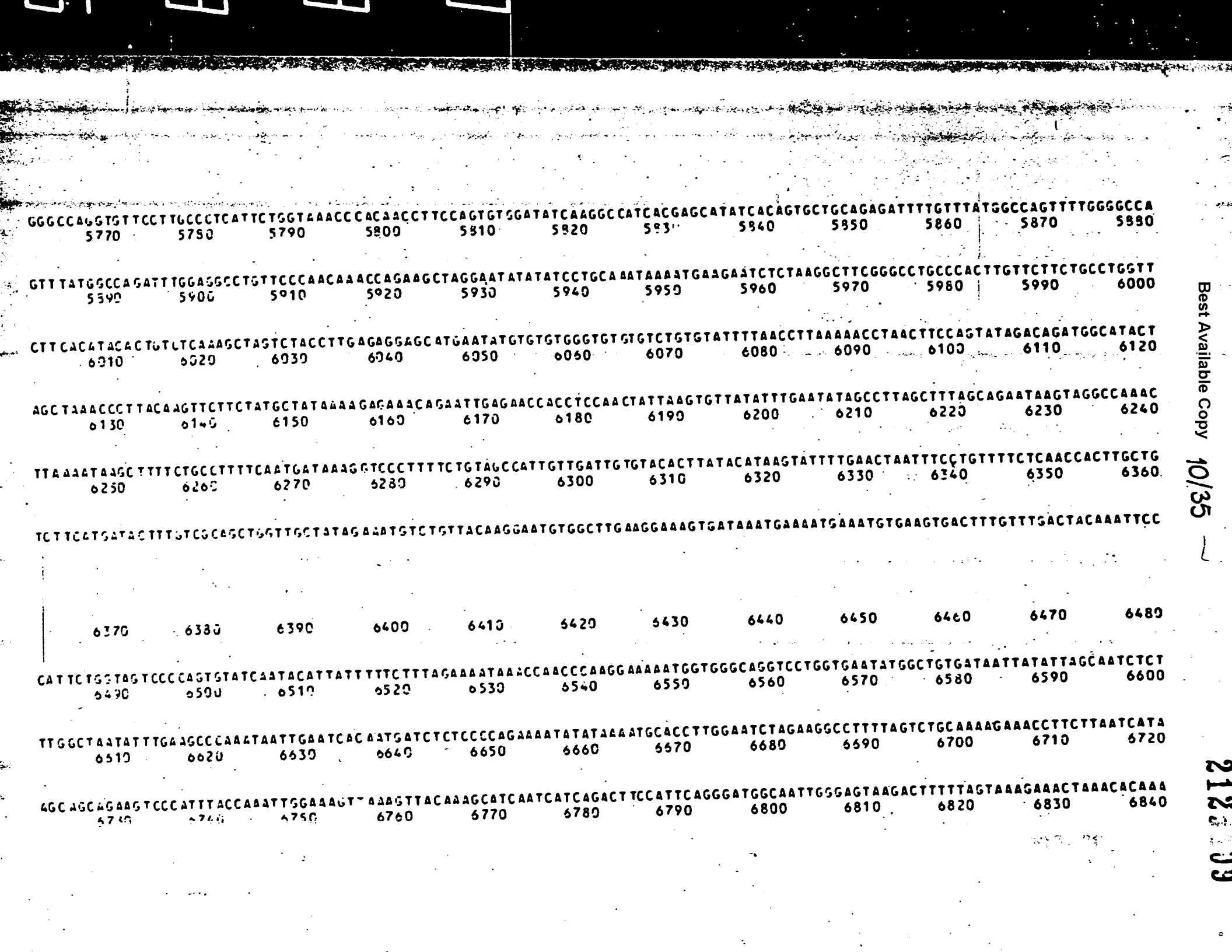

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GTCATTAGACTCTGTAAAAGTCTTACCAAATTTGATTCTGGAACACCTATTCTATTTCCGTAAAGATGATGAATTCCGGAGCCAAATGTTCTTTTCATGAAGGATTTGAAAACTGTCCAT
      6850      6860      6870      6880      6890      6900      6910      6920      6930      6940      6950      6960

GAAAATAAGCGCAATCAACCTTTTAGCTTGAGACTCTATTCACTGATTAGATTTTTTTAAATACTGATGGGCC GCTTCTCAGAAGTGACAAGGATGGGCCTCAATCTCAATTTTTGTAAT
      6970      6980      6990      7000      7010      7020      7030      7040      7050      7060      7070      7080

                                                                  V  P  F  P  C  G  R  V  S  V  S  Q  T  S  K  L  T  R  A  E  A
ACATGTTCCATTTGCCAATGAGAAATATCAGGTTACTAATTTTTCTTCTATTTTTCTAGTGCCATTTCCATGTGGAAGAGTTTCTGTTTCACAAACTTCTAAGCTCACCCGTGCTGAGGC
      7090      7100      7110      7120      7130      7140      7150      7160      7170      7180      7190      7200

  V  F  P  D  V  D  Y  V  N  S  T  E  A  E  T  I  L  D  N  I  T  Q  S  T  Q  S  F  N  D  F  T  R  V  V  G  G  E  D  A  K
TGTTTTTCCTGATGTGGACTATGTAAATTCTACTGAAGCTGAAACCATTTTGGATAACATCACTCAAAGCACCCAATCATTTAATGACTTCACTCGGGTTGTTGGTGGAGAAGATGCCAA
      7210      7220      7230      7240      7250      7260      7270      7280      7290      7300      7310      7320

  P  G  Q  F  P  N  Q
ACCAGGTCAATTCCCTTGGCAGGTACTTTATACTGATGGTGTGTCAAAACTGGAGCTCAGCTGGCAAGACACAGGCCAGGTGGGAGACTGAGGCTATTTTACTAGACAGACCTATTGGGA
      7330      7340      7350      7360      7370      7380      7390      7400      7410      7420      7430      7440

TGTGAGAAGTATTTAGGCAAGTTTCAGCACTAACCAATGTGAGAAGGCCTCCAGAGATGAGCAGTTGGTGAAAGAGAGGCTCAAAACCAGCTACCATACAGGTCAAGAAGAATTTGGCAT
      7450      7460      7470      7480      7490      7500      7510      7520      7530      7540      7550      7560

TAAGGAAACAGCATAGCAGGATTCCAGACAGGCA---GGTCAACAACATGAAGGTCTGGAAGAAAGGTCGCAGGTACTCAGGTTCAGGGCACTACTTCAGCTTCAGCCCTTGCAAAAACT
      7570      7580      7590      7600      7610      7620      7630      7640      7650      7660      7670      7680

GGTGAGAGTTGGAAAGTCTTTAGGCTAAGAAAAATTGGATTATTTAAAAGGGGGTAAAGAAAGGGACTCAAGGAGGAAGGATTAAGGCAAGAACTAGGTT-CAAGAACAGGGCATGAGAG
      7690      7700      7710      7720      7730      7740      7750      7760      7770      7780      7790      7800

AGAGTCTTGATCTACCACTATAGTTCTCGT----------------------------------------------------------------GGAACTGAACGGAGATTACT
      7810      7820      7830      7840      7850      7860      7870      7880      7890      7900      7910      7920

TAACCGA-ATTTGA-AAC-CCTGG-CAACACG-CGAACCCCACCTCTAATTAAAAAAAATACAAAATTAGCTAGGTGTGATGACTCCCACCTGTGCTCCCAGCTATTCAGGAGGCTGAGG
      7930      7940      7950      7960      7970      7980      7990      8000      8010      8020      8030      8040
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FIG. 7A

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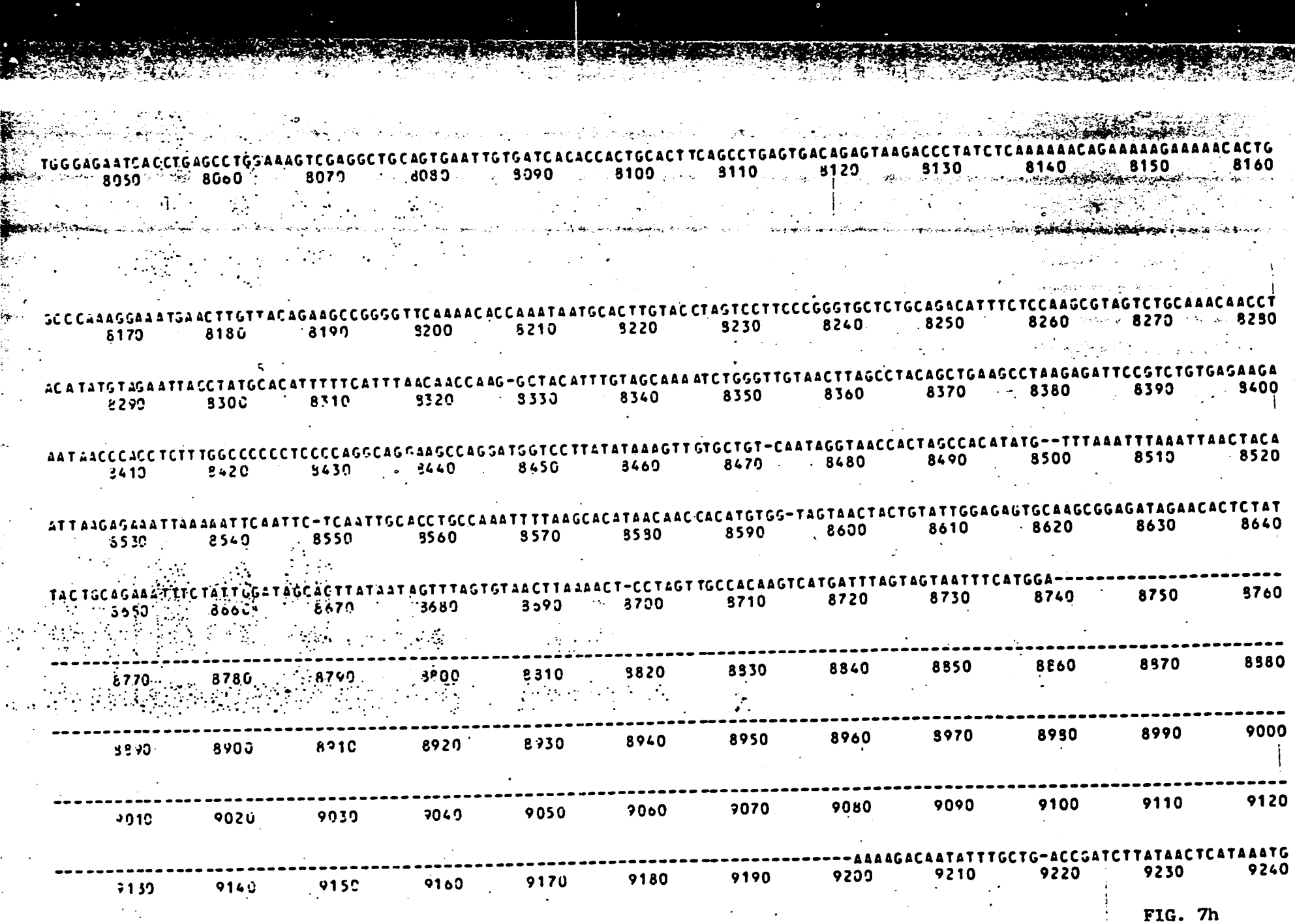

FIG. 7h

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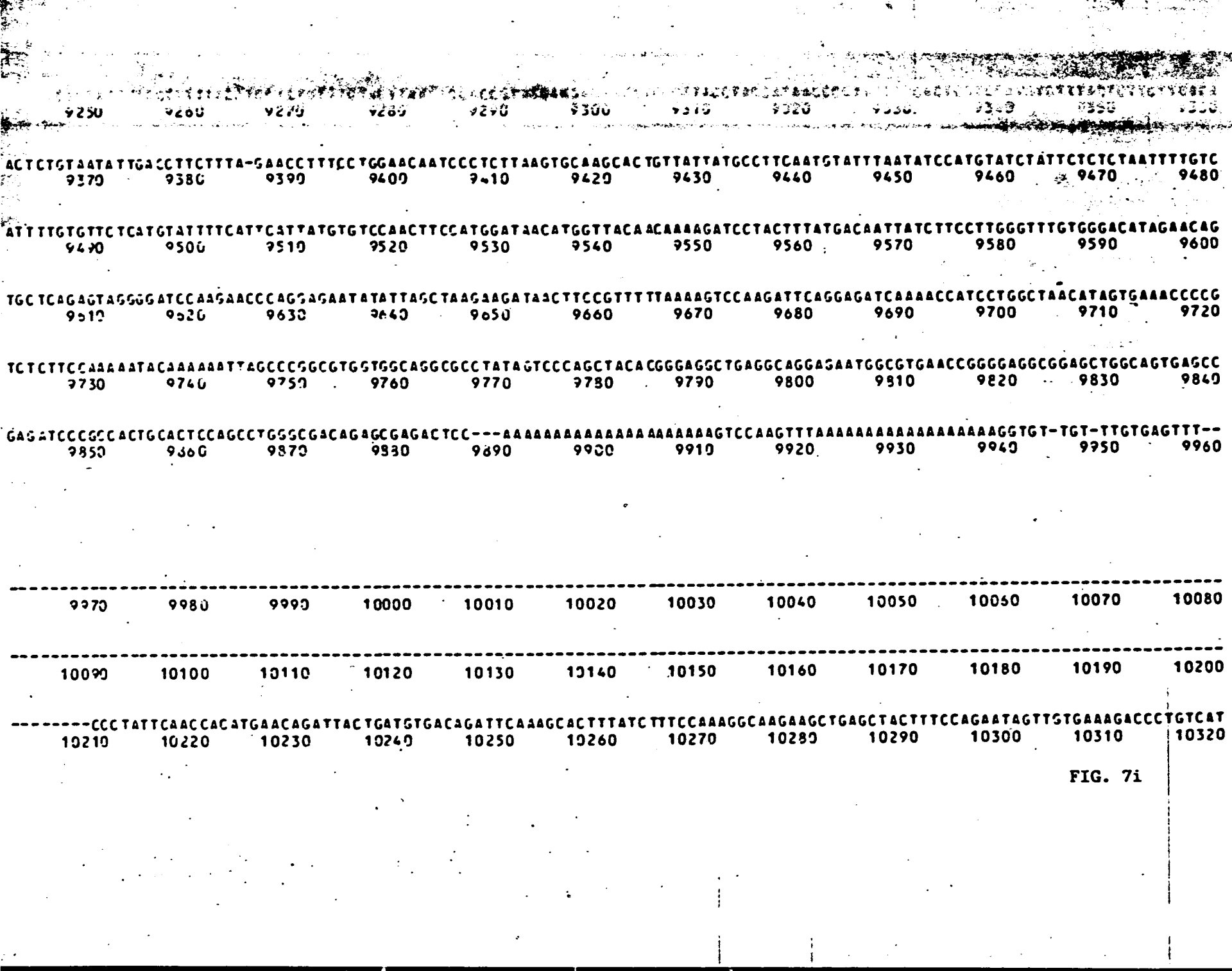

FIG. 7i

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FIG. 7j

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GCTCCTTGAGAACTCGGGAAAGGAAGCAGGGTCTCTGAAGAAATACTTCAGGAGTAGAAAGAGGAAGCTAGAGGGTTAAATGCACTACACAGGAACAGAAATGAGTTTTTCTTAGAGTTA

11530 11540 11550 11560 11570 11580 11590 11600 11610 11620 11630 11640

GTATATGTCTAGAGGTGTAGTAAACTAAAACAAGTCTTGAATTGCATACCGCCACGTAGGGAAGAAATGAAAACCTTTGAATATTAGTGAAAAAAGGGAAACTGCAACGCCTGTATTACT

11650 11660 11670 11680 11690 11700 11710 11720 11730 11740 11750 11760

AGATAGCTTTCATCAACAGCTCAAAACCGACAGATTTAAAGAAGCAACACCGCATTTTGGCTTTCTAAAGCTTTAATTTGGTTTGGATCCCATGCCCATGACCCTGCCAGCTG

11770 11780 11790 11800 11810 11820 11830 11840 11850 11860 11870

FIG. 7k

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FIG. 8(a)

→ 1	0.000	ECOR1	GAATTC
30	0.002	HINF1	GAATC
33	0.003	MBO11	TCTTC
46	0.004	ALU1	AGCT
48	0.004	DDE1	CTGAG
50	0.004	MNL1	GAGG
89	0.007	MNL1	CCTC
94	0.008	MST1	TGCGCA
95	0.008	MHA1	GCGC
112	0.009	MBO1	GATC
120	0.010	BBV1	GCAGC
120	0.010	FNU4H1	GCAGC
123	0.010	BBV1	GCAGC
123	0.010	FNU4H1	GCAGC
134	0.011	DDE1	CTGAG
148	0.012	HPH1	GGTGA
173	0.014	MNL1	GAGG
191	0.016	DDE1	CTTAG
204	0.017	HINF1	GAATC
247	0.021	SPH1	GCATGC
265	0.022	ALU1	AGCT
266	0.022	BBV1	GCTGC
266	0.022	FNU4H1	GCTGC
305	0.026	XMN1	GAACACTTTC
376	0.032	ALU1	AGCT
417	0.035	MNL1	GAGG
425	0.036	STU1	AGGCCT
426	0.036	HAE111	GGCC
465	0.039	RSA1	GTAC
486	0.041	DDE1	CTTAG
517	0.043	ALU1	AGCT
523	0.044	ALU1	AGCT
559	0.047	MNL1	CCTC
578	0.049	RSA1	GTAC
590	0.050	DDE1	CTAAG
621	0.052	ALU1	AGCT
652	0.055	HINF1	GATTC
→ 732	0.062	HIND111	AAGCTT
733	0.062	ALU1	AGCT
781	0.066	MBO11	GAAGA
788	0.066	MNL1	GAGG
816	0.069	MNL1	GAGG

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FIG. 8(b)

818	0.069	FOK1	GGATG
898	0.076	MNL1	CCTC
898	0.076	MST11	CCTCAGG
899	0.076	DDE1	CTCAG
913	0.077	DDE1	CTGAG
929	0.078	HPH1	GGTGA
976	0.082	TAQ1	TCGA
1027	0.086	RSA1	GTAC
1032	0.087	MNL1	GAGG
1054	0.089	MNL1	CCTC
→ 1072	0.090	HIND111	AAGCTT
1073	0.090	ALU1	AGCT
1099	0.092	BBV1	GCAGC
1099	0.092	FNU4H1	GCAGC
1101	0.093	ALU1	AGCT
1138	0.096	MNL1	GAGG
1145	0.096	HINC11	GTTGAC
1150	0.097	FOK1	CATCC
1161	0.098	ALU1	AGCT
1167	0.098	HPH1	TCACC
1193	0.100	HPH1	GGTGA
1198	0.101	ALU1	AGCT
1200	0.101	DDE1	CTGAG
1204	0.101	MBO11	GAAGA
1226	0.103	MNL1	GACG
1284	0.108	DDE1	CTGAG
1286	0.108	MNL1	GAGG
1323	0.111	RSA1	GTAC
1365	0.115	BBV1	GCTGC
1365	0.115	FNU4H1	GCTGC
1370	0.115	XBA1	TCTAGA
1424	0.120	DDE1	CTAAG
1427	0.120	ALU1	AGCT
1449	0.122	RSA1	GTAC
1603	0.135	ALU1	AGCT
1626	0.137	ACC1	GTATAC
1633	0.137	HINC11	GGTTAAC
[illegible]	[illegible]	[illegible]	[illegible]
1670	0.141	MNL1	GAGG
1672	0.141	HAE111	GGCC
1685	0.142	FOK1	GGATG
1759	0.148	HINF1	GATTC
1766	0.149	MNL1	GAGG
1841	0.155	SAU961	GGGCC
1842	0.155	HAE111	GGCC

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FIG. 8(c)

1855	0.156	DDE1	CTTAG
1884	0.159	MBO11	TCTTC
1901	0.160	AVA11	GGACC
1901	0.160	SAU961	GGACC
1939	0.163	MNL1	CCTC
1940	0.163	DDE1	CTCAG
1947	0.164	ALU1	AGCT
1965	0.165	HAE111	GGCC
1965	0.165	SAU961	GGCCC
2030	0.171	RSA1	GTAC
2081	0.175	RSA1	GTAC
2097	0.177	HGA1	GACGC
2110	0.178	ALU1	AGCT
2112	0.178	DDE1	CTCAG
2116	0.178	RSA1	GTAC
2128	0.179	MBO1	GATC
2141	0.180	MNL1	CCTC
2147	0.181	MNL1	CCTC
2150	0.181	FOK1	CATCC
2158	0.182	MNL1	CCTC
2161	0.182	MNL1	CCTC
2165	0.182	MNL1	CCTC
2171	0.183	ACC1	GTAGAC
2174	0.183	HINF1	GACTC
2222	0.187	DDE1	CTTAG
2225	0.187	ALU1	AGCT
2248	0.189	PST1	CTGCAG
2282	0.192	MST11	CCTAAGG
2283	0.192	DDE1	CTAAG
2287	0.193	FOK1	GGATG
2296	0.193	MNL1	CCTC
2301	0.194	ALU1	AGCT
2349	0.198	BBV1	GCTGC
2349	0.198	FNU4H1	GCTGC
2422	0.204	HINF1	GATTC
2468	0.208	HINF1	GATTC
2483	0.209	BSTE11	GGTAACC
2503	0.211	ALU1	AGCT
2524	0.212	XBA1	TCTAGA
2534	0.213	DDE1	CTAAG

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FIG. 8(d)

2658	0.224	RSA1	GTAC
2678	0.225	SFNA1	GCATC
2726	0.230	HINF1	GAGTC
2728	0.230	HINC11	GTCAAC
2770	0.233	HINF1	GATTC
2807	0.236	HGA1	GACGC
2811	0.237	DDE1	CTTAG
2965	0.250	HINF1	GATTC
2984	0.251	AVA11	GGTCC
2984	0.251	SAU961	GGTCC
3012	0.254	MNL1	GAGG
3024	0.255	HINF1	GATTC
3032	0.255	ALU1	AGCT
3048	0.257	NDE1	CATATG
3090	0.260	MNL1	GAGG
3093	0.260	MBO11	GAAGA
3106	0.262	RSA1	GTAC
3141	0.264	TAQ1	TCGA
3168	0.267	RSA1	GTAC
3193	0.269	MBO1	GATC
3213	0.271	HGIA1	GTGCTC
3216	0.271	DDE1	CTCAG
3220	0.271	MBO11	GAAGA
3234	0.272	RSA1	GTAC
3263	0.275	MNL1	GAGG
3333	0.281	NDE1	CATATG
3412	0.287	BCL1	TGATCA
3413	0.287	MBO1	GATC
3415	0.288	HPH1	TCACC
3457	0.291	DDE1	CTAAG
3462	0.292	HINF1	GACTC
3489	0.294	TAQ1	TCGA
3522	0.297	ECOR5	GATATC
3585	0.302	RSA1	GTAC
→ 3624	0.305	BGL11	AGATCT
3625	0.305	MBO1	GATC
3638	0.306	MBO1	GATC
3689	0.311	HPH1	TCACC
3792	0.319	ALU1	AGCT

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FIG. 8(e)

3847	0.324	RSA1	GTAC
3905	0.329	RSA1	GTAC
3970	0.334	BSTN1	CCAGG
3970	0.334	SCRF1	CCAGG
3979	0.335	BSTE11	GGTAACC
4016	0.338	MNL1	GAGG
4022	0.339	SFNA1	GCATC
4025	0.339	MBO11	TCTTC
4368	0.368	HINF1	GAGTC
4384	0.369	RSA1	GTAC
4410	0.371	SFNA1	GATGC
4469	0.376	SFNA1	GATGC
4520	0.381	RSA1	GTAC
4523	0.381	DDE1	CTGAG
4525	0.381	MNL1	GAGG
4529	0.381	ECOR5	GATATC
4533	0.382	TAQ1	TCGA
4658	0.392	HINF1	GAATC
4695	0.395	ALU1	AGCT
4719	0.397	XBA1	TCTAGA
4727	0.398	SFNA1	GCATC
→ 4769	0.402	ECOR1	GAATTC
4769	0.402	XMN1	GAATTCTTTC
4778	0.402	DDE1	CTGAG
4780	0.403	HINF1	GAGTC
4848	0.408	NDE1	CATATG
4961	0.418	HINF1	GATTC
4988	0.420	DDE1	CTGAG
5020	0.423	ALU1	AGCT
5022	0.423	DDE1	CTGAG
5049	0.425	HINF1	GATTC
5053	0.426	HPA11	CCGG
5085	0.428	BCL1	TGATCA
5086	0.428	MBO1	GATC
→ 5157	0.434	PVU11	CAGCTG
5158	0.434	ALU1	AGCT
5225	0.440	ACC1	GTAGAC
5258	0.443	PST1	CTGCAG
5285	0.445	MNL1	GAGG
5339	0.450	ECOR5	GATATC
5355	0.451	RSA1	GTAC
5367	0.452	HGIA1	GTGCAC
5394	0.454	RSA1	GTAC
5402	0.455	DDE1	CTCAG
5414	0.456	BSTN1	CCAGG

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FIG. 8(f)

5414	0.456	SCRF1	CCAGG
5421	0.456	MBO11	GAAGA
5451	0.459	MBO1	GATC
5455	0.459	ALU1	AGCT
5481	0.462	FNU4H1	GCGGC
5490	0.462	MNL1	GAGC
5560	0.468	ALU1	AGCT
5562	0.468	DDE1	CTGAG
5627	0.474	XMN1	GAAAGTATTC
5653	0.476	FOK1	GGATG
5657	0.476	HINF1	GAGTC
5672	0.478	PST1	CTGCAG
5674	0.478	BBV1	GCAGC
5674	0.478	FNU4H1	GCAGC
5754	0.485	BSTN1	CCTGG
5754	0.485	SCRF1	CCTGG
5761	0.485	SAU961	GGGCC
5762	0.485	HAE111	GGCC
5764	0.485	BSTN1	CCAGG
5764	0.485	SCRF1	CCAGG
5779	0.487	MNL1	CCTC
5813	0.490	ECOR5	GATATC
5821	0.490	HAE111	GGCC
5844	0.492	BBV1	GCTGC
5844	0.492	FNU4H1	GCTGC
5845	0.492	PST1	CTGCAG
5863	0.494	BAL1	TGGCCA
5864	0.494	HAE111	GGCC
5875	0.495	SAU961	GGGCC
5876	0.495	HAE111	GGCC
5886	0.496	BAL1	TGGCCA
5887	0.496	HAE111	GGCC
5898	0.497	MNL1	GAGG
5899	0.497	STU1	AGGCCT
5900	0.497	HAE111	GGCC
5922	0.499	ALU1	AGCT
5952	0.501	MBO11	GAAGA
5955	0.501	HINF1	GAATC
5961	0.502	DDE1	CTAAG
5971	0.503	SAU961	GGGCC

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FIG. 8(g)

5972	0.503	HAE111	GGCC
5987	0.504	MBO11	TCTTC
5994	0.505	BSTN1	CCTGG
5994	0.505	SCRF1	CCTGG
6000	0.505	MBO11	TCTTC
6021	0.507	ALU1	AGCT
6026	0.507	ACC1	GTCTAC
6037	0.508	MNL1	GAGG
6121	0.515	ALU1	AGCT
6139	0.517	MBO11	TCTTC
6177	0.520	MNL1	CCTC
6211	0.523	DDE1	CTTAG
6214	0.523	ALU1	AGCT
6233	0.525	HAE111	GGCC
→ 6248	0.526	HIND111	AAGCTT
6249	0.526	ALU1	AGCT
6275	0.528	AVA11	GGTCC
6275	0.528	SAU961	GGTCC
6305	0.531	RSA1	GTAC
6361	0.536	MBO11	TCTTC
6370	0.537	BBV1	GCAGC
6379	0.537	FNU4H1	GCAGC
→ 6380	0.537	PVU11	CAGCTG
6381	0.537	ALU1	AGCT
6558	0.552	AVA11	GGTCC

6558	0.552	SAU961	GGTCC
6561	0.553	BSTN1	CCTGG
6561	0.553	SCRF1	CCTGG
6564	0.553	HPH1	GGTGA
6629	0.558	HINF1	GAATC
6639	0.559	MBO1	GATC
6674	0.562	HINF1	GAATC
6677	0.562	XBA1	TCTAGA
6683	0.563	STU1	AGGCCT
6684	0.563	HAE111	GGCC
6722	0.566	BBV1	GCAGC
6722	0.566	FNU4H1	GCAGC
6767	0.570	SFNA1	GCATC
6793	0.572	FOK1	GGATG
6848	0.577	HINF1	GACTC

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FIG. 8(h)

6874	0.579	HINF1	GATTC
6911	0.582	ECOR1	GAATTC
6916	0.582	HPA11	CCGG
6984	0.588	ALU1	AGCT
6991	0.589	HINF1	GACTC
7028	0.592	SAU961	GGGCC
7029	0.592	HAE111	GGCC
7038	0.593	DDE1	CTCAG
7052	0.594	FOK1	GGATG
7056	0.594	SAU961	GGGCC
7057	0.594	HAE111	GGCC
7059	0.594	MNL1	CCTC
7124	0.600	MBO11	TCTTC
7155	0.603	MBO11	GAAGA
7155	0.603	XMN1	GAAGAGTTTC
7179	0.605	DDE1	CTAAG
7182	0.605	ALU1	AGCT
7185	0.605	HPH1	TCACC
7194	0.606	DDE1	CTGAG
7196	0.606	MNL1	GAGG
7237	0.609	ALU1	AGCT
7293	0.614	AVA1	CTCGGG
7310	0.616	MBO11	GAAGA
7313	0.616	SFNA1	GATGC
7322	0.617	BSTN1	CCAGG
7322	0.617	SCRF1	CCAGG
7343	0.618	RSA1	GTAC
7373	0.621	HGIA1	GAGCTC
7373	0.621	SAC1	GAGCTC
7374	0.621	ALU1	AGCT
7376	0.621	DDE1	CTCAG
→ 7378	0.621	PVU11	CAGCTG
7379	0.621	ALU1	AGCT
7394	0.623	HAE111	GGCC
7396	0.623	BSTN1	CCAGG
7396	0.623	SCRF1	CCAGG
7408	0.624	DDE1	CTGAG
7410	0.624	MNL1	GAGG
7438	0.626	FOK1	GGATG
7485	0.630	STU1	AGGCCT
7486	0.630	HAE111	GGCC
7488	0.631	MNL1	CCTC
7507	0.632	HPH1	GGTGA
7516	0.633	MNL1	GAGG
7529	0.634	ALU1	AGCT
7547	0.636	MBO11	GAAGA

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FIG. 8(i)

7580	0.638	HINF1	GATTC
7599	0.640	HINC11	GTCAAC
7619	0.642	MBO11	GAAGA
7634	0.643	RSA1	GTAC
7637	0.643	DDE1	CTCAG
7659	0.645	ALU1	AGCT
7681	0.647	HPH1	GGTGA
7705	0.649	DDE1	CTAAG
7745	0.652	HINF1	GACTC
7753	0.653	MNL1	GAGG
7802	0.657	HINF1	GAGTC
7809	0.658	MBO1	GATC
7940	0.669	BSTN1	CCTGG
7940	0.669	SCRF1	CCTGG
7963	0.671	MNL1	CCTC
7989	0.673	ALU1	AGCT
8002	0.674	HINF1	GACTC
8013	0.675	HGIA1	GTGCTC
8021	0.675	ALU1	AGCT
8031	0.676	MNL1	GAGG
8035	0.677	DDE1	CTGAG
8037	0.677	MNL1	GAGG
8046	0.678	HINF1	GAATC
8049	0.678	HPH1	TCACC
8053	0.678	DDE1	CTGAG
8058	0.679	BSTN1	CCTGG
8058	0.679	SCRF1	CCTGG
8067	0.679	TAQ1	TCGA
8069	0.680	MNL1	GAGG
8072	0.680	BBV1	GCTGC
8072	0.680	ENU4H1	GCTGC
8073	0.680	PST1	CTGCAG
8086	0.681	BCL1	TGATCA
8087	0.681	MBO1	GATC
8109	0.683	DDE1	CTGAG
8160	0.687	HAE111	GGCC
8160	0.687	SAU961	GGCCC
8190	0.690	HPA11	CCGG

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FIG. 8(j)

8190	0.690	NCI1	CCGGG
8190	0.690	SCRF1	CCGGG
8220	0.692	RSA1	GTAC
8233	0.693	AVA1	CCCGGG
8233	0.693	NCI1	CCCGG
8233	0.693	SCRF1	CCCGG
8233	0.693	SMA1	CCCGGG
8234	0.693	HPA11	CCGG
8234	0.693	NCI1	CCGGG
8234	0.693	SCRF1	CCGGG
8238	0.694	HGIA1	GTGCTC
8243	0.694	PST1	CTGCAG
8282	0.697	NDE1	CATATG
8357	0.704	DDE1	CTTAG
8366	0.705	PVU11	CAGCTG
8367	0.705	ALU1	AGCT
8376	0.705	DDE1	CTAAG
8382	0.706	HINF1	GATTC
8396	0.707	MBO11	GAAGA
8410	0.708	MNL1	CCTC
8417	0.709	HAE111	GGCC
8417	0.709	SAU961	GGCCC
8423	0.709	MNL1	CCTC
8428	0.710	BSTN1	CCAGG
8428	0.710	SCRF1	CCAGG
8440	0.711	BSTN1	CCAGG
8440	0.711	SCRF1	CCAGG
8443	0.711	FOK1	GGATG
8447	0.711	AVA11	GGTCC
8447	0.711	SAU961	GGTCC
8477	0.714	BSTE11	GGTAACC
8492	0.715	NDE1	CATATG
8643	0.728	PST1	CTGCAG
9221	0.777	MBO1	GATC
9263	0.780	MNL1	CCTC
9266	0.780	MNL1	CCTC
9294	0.783	MNL1	GAGG
9335	0.786	FOK1	CATCC
9350	0.787	MBO11	TCTTC

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FIG. 8(k)

9353	0.788	MBO11	TCTTC
9394	0.791	BSTN1	CCTGG
9394	0.791	SCRF1	CCTGG
9406	0.792	MNL1	CCTC
9550	0.804	MBO1	GATC
9571	0.806	MBO11	TCTTC
9600	0.808	HGIA1	GTGCTC
9603	0.809	DDE1	CTCAG
→ 9614	0.810	BAMH1	GGATCC
9615	0.810	MBO1	GATC
9626	0.811	BSTN1	CCAGG
9626	0.811	SCRF1	CCAGG
9641	0.812	ALU1	AGCT
9643	0.812	DDE1	CTAAG
9647	0.812	MBO11	GAAGA
9676	0.815	HINF1	GATTC
9687	0.816	MBO1	GATC
9694	0.816	FOK1	CATCC
9697	0.817	BSTN1	CCTGG
9697	0.817	SCRF1	CCTGG
9723	0.819	MBO11	TCTTC
9747	0.821	NCI1	CCCGG
9747	0.821	SCRF1	CCCGG
9748	0.821	HPA11	CCGG
9762	0.822	HAE11	GGCGCC
9762	0.822	NAR1	GGCGCC
9763	0.822	HHA1	GCGC
9777	0.823	ALU1	AGCT
9787	0.824	MNL1	GAGG
9791	0.825	DDE1	CTGAG
9793	0.825	MNL1	GAGG
9814	0.826	HPA11	CCGG
9814	0.826	NCI1	CCGGG
9814	0.826	SCRF1	CCGGG
9819	0.827	MNL1	GAGG
9826	0.828	ALU1	AGCT
9843	0.829	MBO1	GATC
9864	0.831	BSTN1	CCTGG
9864	0.831	SCRF1	CCTGG
9881	0.832	HINF1	GACTC
10246	0.863	HINF1	GATTC
10279	0.866	ALU1	AGCT
10281	0.866	DDE1	CTGAG
10284	0.866	ALU1	AGCT
10310	0.868	TTH1111	GACCCTGTC

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FIG. 8(L)

10336	0.870	MNL1	CCTC
10347	0.871	MNL1	CCTC
10351	0.872	FOK1	CATCC
10455	0.880	HINF1	GAATC
10463	0.881	MNL1	CCTC
10473	0.882	FOK1	GGATG
10477	0.882	SAU961	GGGCC
10478	0.882	HAE111	GGCC
10482	0.883	ALU1	AGCT
10505	0.885	PST1	CTGCAG
10512	0.885	MNL1	GAGG
10536	0.887	MBO1	GATC
10543	0.888	PST1	CTGCAG
10545	0.888	BBV1	GCAGC
10545	0.888	FNU4H1	GCAGC
10563	0.890	DDE1	CTAAG
10568	0.890	SFNA1	GCATC
10589	0.892	PVU11	CAGCTG
10590	0.892	ALU1	AGCT
10605	0.893	HPH1	GGTGA
10625	0.895	ALU1	AGCT
10656	0.897	HPH1	TCACC
10685	0.900	SFNA1	GATGC
10698	0.901	MBO11	TCTTC
10733	0.904	BSTN1	CCAGG
10733	0.904	SCRF1	CCAGG
10751	0.905	BCL1	TGATCA
10752	0.905	MBO1	GATC
10760	0.906	HPH1	GGTGA
10763	0.906	MBO11	GAAGA
10779	0.908	MBO11	GAAGA
10865	0.915	HPH1	GGTGA
10869	0.915	ALU1	AGCT
10899	0.918	MBO11	GAAGA
10925	0.920	HPH1	GGTGA
10950	0.922	HINF1	GATTC
10958	0.923	MNL1	CCTC
11015	0.928	BBV1	GCAGC

FIG. 8(m)

11015	0.928	FNU4H1	GCAGC
11061	0.932	HINC11	GTTGAC
11073	0.933	ALU1	AGCT
11095	0.934	FNU4H1	GCGGC
11132	0.938	HPH1	TCACC
11135	0.938	BSTN1	CCTGG
11135	0.938	SCRF1	CCTGG
11137	0.938	BAL1	TGGCCA
11138	0.938	HAE111	GGCC
11145	0.939	MBO1	GATC
11157	0.940	DDE1	CTAAG
11170	0.941	BAMH1	GGATCC
11171	0.941	MBO1	GATC
11181	0.942	ALU1	AGCT
11256	0.948	BSTN1	CCAGG
11256	0.948	SCRF1	CCAGG
11265	0.949	HPH1	TCACC
11268	0.949	MNL1	CCTC
11269	0.949	DDE1	CTCAG
11272	0.949	ALU1	AGCT
11278	0.950	BSTN1	CCAGG
11278	0.950	SCRF1	CCAGG
11300	0.952	BBV1	GCAGC

11300	0.952	FNU4H1	GCAGC
11303	0.952	FNU4H1	GCCGC
11314	0.953	NRU1	TCGCGA
11315	0.953	FNUD11	CGCG
11324	0.954	ALU1	AGCT
11330	0.954	BSTN1	CCAGG
11330	0.954	SCRF1	CCAGG
11349	0.956	HPA11	CCGG
11356	0.956	HAE11	GGCGCT
11357	0.956	HHA1	GCGC
11367	0.957	FOK1	CATCC
11381	0.958	MNL1	CCTC
11428	0.962	FNUD11	CGCG
11429	0.963	HHA1	GCGC
11447	0.964	HPA11	CCGG
11464	0.965	MNL1	GAGG

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FIG. 8(n)

11466	0.966	HAE111	GGCC
11478	0.967	MNL1	GAGG
11481	0.967	RSA1	GTAC
11494	0.968	MNL1	CCTC
11497	0.968	BSTN1	CCAGG
11497	0.968	SCRF1	CCAGG
11500	0.968	HAE111	GGCC
11500	0.968	SAU961	GGCCC
11504	0.969	FNUD11	CGCG
11505	0.969	HHA1	GCGC
11506	0.969	FNUD11	CGCG
11515	0.970	DDE1	CTCAG
11519	0.970	HGIA1	GAGCTC
11519	0.970	SAC1	GAGCTC
11520	0.970	ALU1	AGCT
11533	0.971	AVA1	CTCGGG
11557	0.973	MBO11	GAAGA
11560	0.974	XMN1	GAAATACTTC
11581	0.975	MNL1	GAGG
11586	0.976	ALU1	AGCT
11591	0.976	MNL1	GAGG
11631	0.980	DDE1	CTTAG
11648	0.981	XBA1	TCTAGA
11652	0.981	MNL1	GAGG
11701	0.985	MBO11	GAAGA
11765	0.991	ALU1	AGCT
11778	0.992	ALU1	AGCT
→ 11828	0.996	HIND111	AAGCTT
11829	0.996	ALU1	AGCT
11845	0.998	BAMH1	GGATCC
11846	0.998	MBO1	GATC
→ 11868	0.999	PVU11	CAGCTG
11869	1.000	ALU1	AGCT

FIG. 9(a)

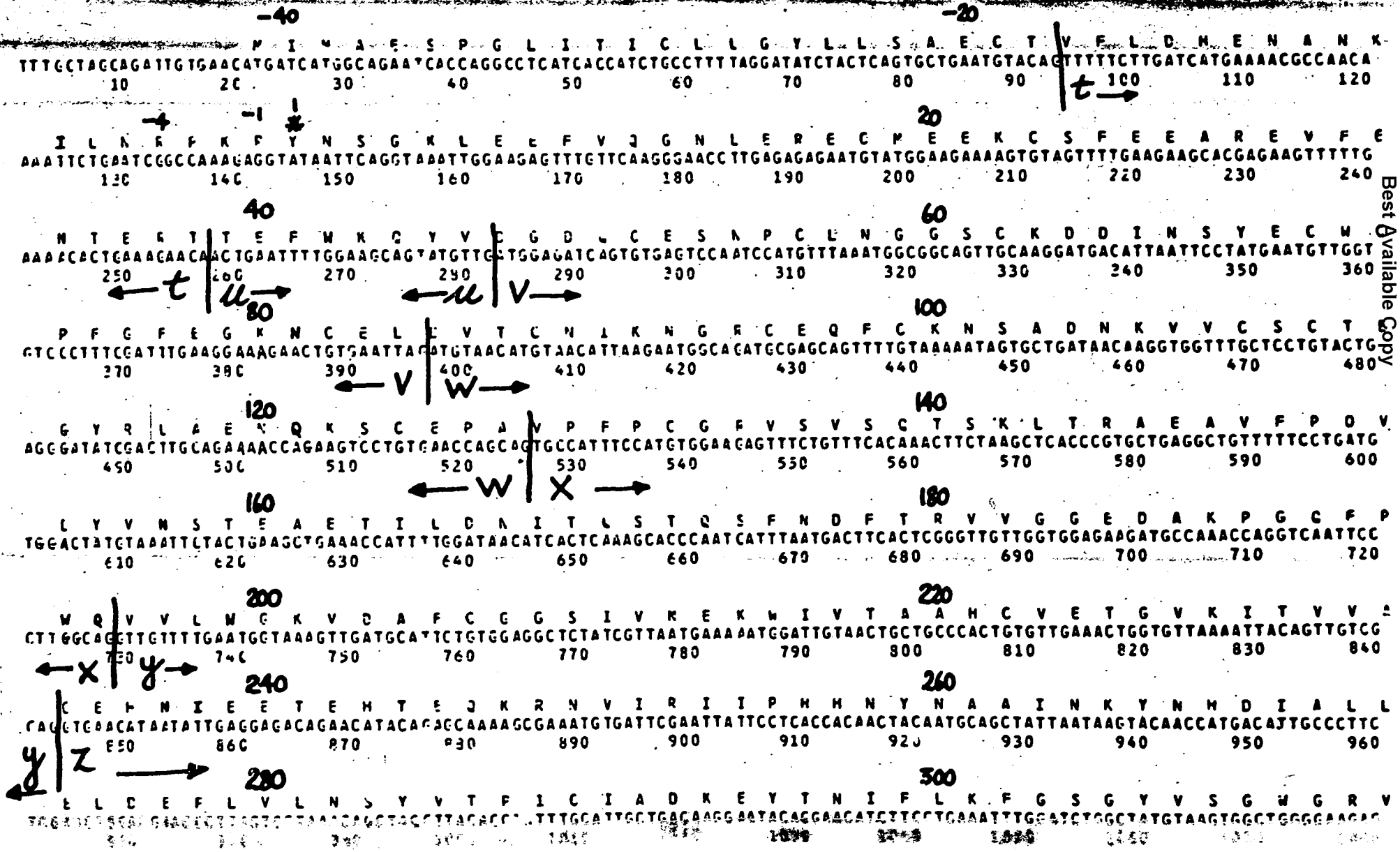

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FIG. 9(b)

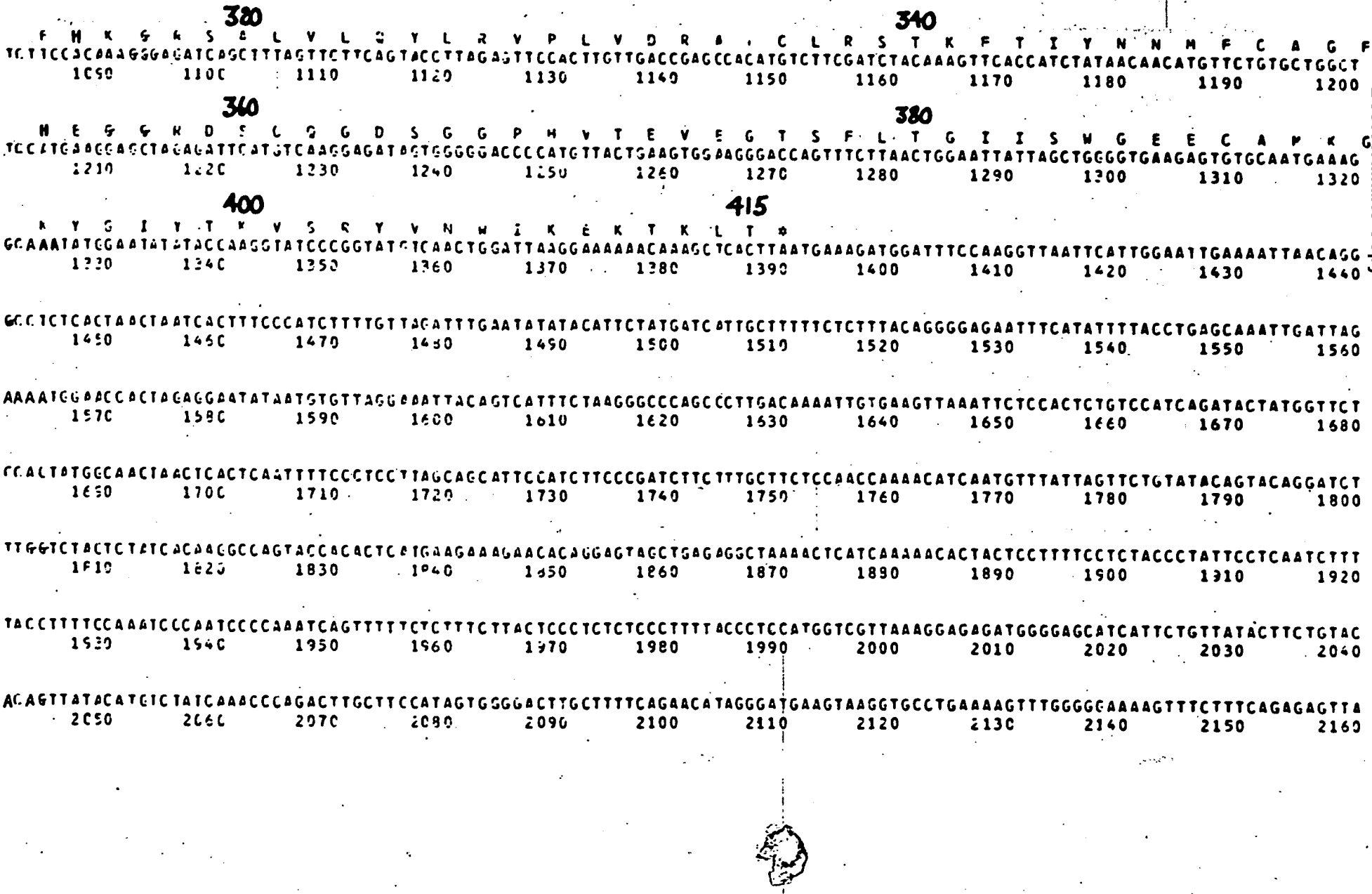

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FIG. 9(c)

AGTTATTTTATATATGTAATATATATATAAAATATATAATATACAATATAAATATATAGTGTGTGTGTGTATGCGTGTGTGTAGACACACACGCATACACACATATAATGGAAGCAATAA
2170 2180 2190 2200 2210 2220 2230 2240 2250 2260 2270 2280

GCCATTCTAAGAGCTTGTATGCTTATGGAGGTCTGACTAGGCATGATTTGACGAAGGCAAGATTGGCATATCATTGTAACTAAAAAAGCTGACATTGACCCAGACATATTGTACTCTTTC
2290 2300 2310 2320 2330 2340 2350 2360 2370 2380 2390 2400

TAAAAATAATAATAATAATGCTAACAGAAAGAAGACAACCGTTCGTTTGCAATCTACAGCTAGTAGAGACTTTGAGGAAGAATTCAACAGTGTGTCTTCAGCAGTGTTCAGAGCCAAGCA
2410 2420 2430 2440 2450 2460 2470 2480 2490 2500 2510 2520

AGAAGTTGAAGTTGCCTAGACCAGAGGACATAAGTGTCATGTCTCCTTTAACTAGCATACCCCGAAGTGGAGAAGGGTGCAGCAGGCTCAAAGGCATAAGTCATTCCAATCAGCCAACTA
2530 2540 2550 2560 2570 2580 2590 2600 2610 2620 2630 2640

AGTTGTCCTTTTCTGGTTTCGTGTTCACCATGGAACATTTTGATTATAGTTAATCCTTCTATCTTGAATCTTCTAGAGAGTTGCTGACCAACTGACGTATGTTTCCCTTTGTGAATTAAT
2650 2660 2670 2680 2690 2700 2710 2720 2730 2740 2750 2760

AAACTGGTGTTCTGGTTCAAA
2770

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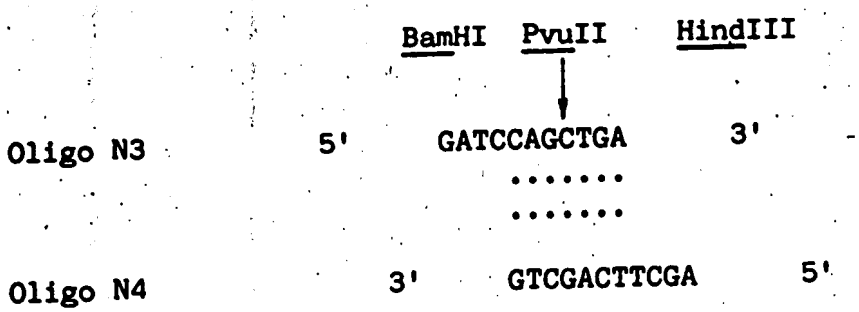

Fig. 10

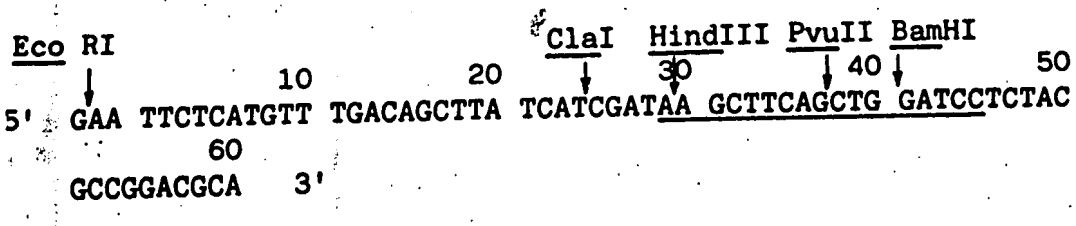

Fig. 11

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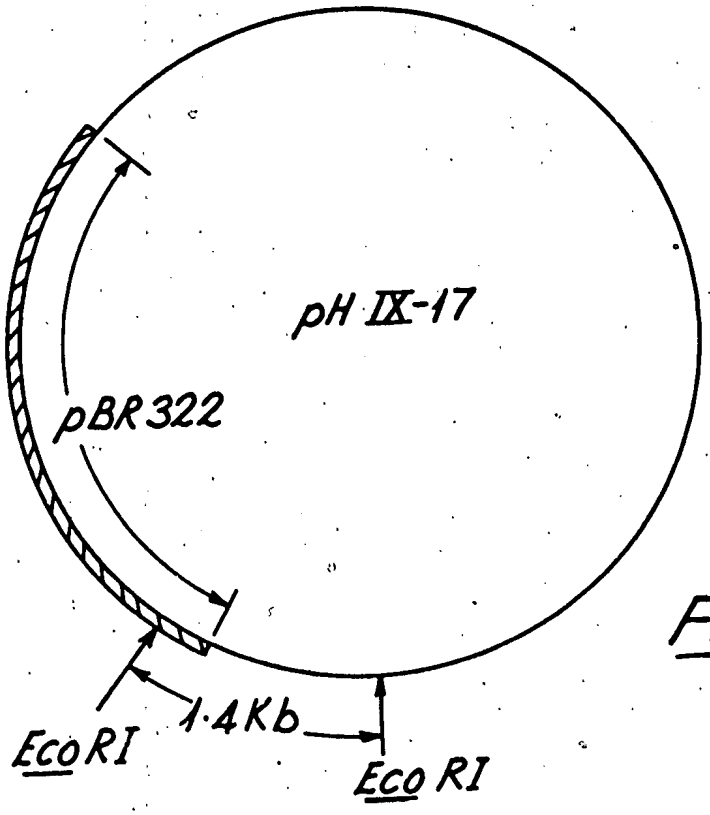

Fig. 12

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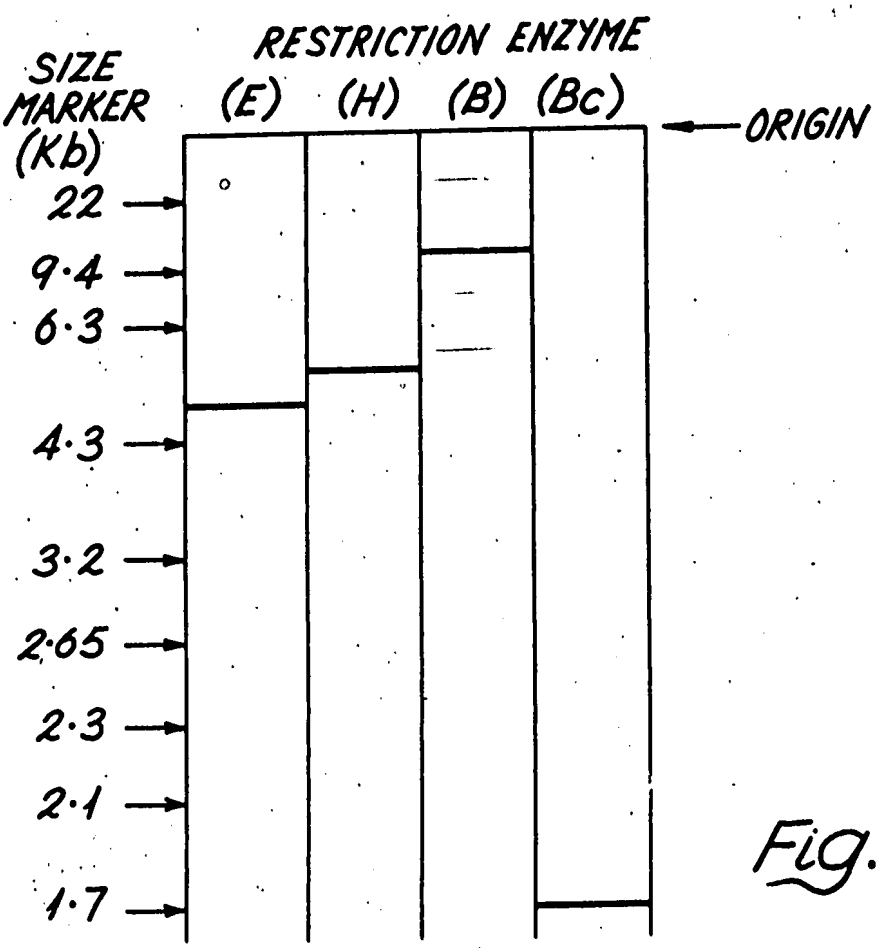

Fig. 13

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